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The Use of Animal Models Assists Researchers in Today's Scientific Discovery

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The use of animal models in biomedical research is critical for continued progress to combat disease and to discover new and better treatments for existing illness and conditions. The vast majority of scientists and researchers involved in medical exploration agree that without the use of animal models, major medical advances would not have been achieved nor would current research techniques be available.

To solve health problems, researchers must have scientific data that is relevant to the human condition. Data from human experiments is the most scientifically relative. But such experimentation, in many cases, is ethically unacceptable. Few people would offer themselves or a family member as the first subject of research to understand and cure diseases such as AIDS or Alzheimer's. The U.S. Government requires that most safety testing be designed and based on results of animal experimentation and a knowledge of the history of the disease or condition under study. After humans, animals offer the most accurate means to assess human biological reactions and responses.

Nonanimal research models are used in research labs across the country whenever possible. Biological models such as cell and tissue cultures, and nonbiological techniques such as mathematical and computer modeling, are used where appropriate. However, since these methods cannot mimic all the complicated interactions that occur in humans or animals, animal testing is still necessary. Knowledge gained from animal research has helped scientists develop many adjunct techniques that are reducing the numbers of animals required.

Impact Study *continued from page 3*

Activity Impact: *Food production research reduces farmers' losses and increases their output.*

Activity:	Research Products:	Economic Impact:
Food Supply Productivity Research	Prevention and treatment of diseases and disorders impairing the productivity of the food industry	$17.7 billion in losses can be avoided or productivity gained in the United States agriculture industry ($714.5 million in Pennsylvania)

Additionally, the research into marine animal medicine at Woods Hole, Massachusetts should have a significant impact on the growing aquaculture and biotechnology industries in the United States and in Pennsylvania.

Activity Impact: *As a result of the School's teaching activities, its alumni increase their earning power.*

Activity:	Teaching Product:	Economic Impact:
	3,400 living VMDs able to earn an additional $ 30,692* per year on average (1,356 VMDs in Pennsylvania)	Additional $104 million expended in the national economy per year, on average ($41.6 million in the Commonwealth of Pennsylvania)

Activity Impact: *The School's services offered through New Bolton Center treat over 24,700 large animals, reducing economic losses.*

Activity:	Service Products:	Economic Impact:
Health Care Services to Large Animals	Nearly 8,700 horses, 14,300 cattle and 1,700 other valuable animals treated	Approximately $239.2 million in losses avoided annually (approximately $157.6 million in Pennsylvania)

Future Potential Impact: *The School is involved in activities which have not yet resulted in specific, exportable products, but could potentially have a significant impact such as:*

- Many sources expect the School to be an important contributor to the biotechnology industry and the aquaculture industry, among others.
- The School's investigators are researching causes, prevention, and treatment for diseases that could potentially affect about 80 million Americans.
- The estimated market for these treatments being researched is over $70 billion annually. Such research breakthroughs will contribute to improved human health and prevention of disease.

The Role of Animals in Current Research and Testing

Biomedical research with animals has four major goals:

- To provide biological knowledge upon which disease prevention can be based;
- To provide models for the study of naturally occurring diseases of humans and animals;
- To test potential therapies, diagnostic and surgical procedures, and medical devices;
- To study the safety and efficacy of new drugs or to determine the potential toxicity of chemicals to which animals will be exposed.

Researchers must understand the biology and physiology of higher organisms before they can make advances in the treatment and prevention of disease. Animal models provide information on the mechanisms of disease and an organism's own defensive response. Scientists study animal models for clues as to how the disease is transmitted and how genetic susceptibility and other factors may predispose an individual to disease. In the case of infectious disease, scientists attempt to isolate the disease-causing agent in the affected animals as the first step toward development of a vaccine.

Data from animal studies is essential before new therapeutic techniques and surgical procedures can be tested on patients. Researchers must use animal models to develop and refine techniques to determine if the techniques will achieve their purpose without risking harm to the patient. Animals are also essential to measure a drug's beneficial or harmful effects on organs and tissue. Moreover, data documenting efficacy and safety is required by the Food and Drug Administration (FDA) before a new drug is approved for testing in clinical trials on humans. Such testing remains the best predictor of adverse risks such as cancer, reproductive disorders and birth defects.

Two of the most controversial tests are the Lethal Dose 50 (LD50) and Draize tests. The LD50 test provides data on how toxic a substance is by determining the dose needed to kill 50 percent of a test group of rodents. The classical LD50 test using large numbers of animals is rarely used today. The maximum tolerable dose is important information for some cancer chemotherapeutic agents where the clinically effective dose is near the lethal dose. The doses that animals tolerate on an acute basis provide information for risk assessment and also determine doses for further studies. Many toxicologists believe that fewer animals can be used to achieve sufficient data, and work is being done to develop nonanimal methods.

There are two Draize tests: one for the eye and one for the skin. The Draize eye irritancy test measures how safe a substance is to the eye by putting drops of a substance on rabbits' eyes. While modifications of this test and alternatives are being explored, many scientists and the FDA believe that this is still one of the best predictors of the effects a chemical would have on the human eye. The skin test is performed in a similar fashion, by exposing a chemical substance to an animal's skin to measure possible irritancy.

Duplication and Validation of Research

Both government and private research institutions practice stringent review processes when approving research projects because of concern for the number of animals used and because of the cost of research. Experts review research proposals to measure the importance of a project, its scientific merit, the competence and the appropriateness of research models.

NIH, the major single source of funding for U.S. biomedical research, requires each grant application to include a bibliography of all relevant scientific literature to avoid unnecessary duplication of research. The cost of research plays a significant role in deciding appropriate ventures. The NIH, for example, is able to fund only about one-third of all research proposals judged worthy of support, and

therefore, selects projects which will have the most impact on human and animal health. Similar research guidelines are used at pharmaceutical companies and universities.

The Salk Institute in LaJolla, CA, one of the world's premier research organizations, is one of many facilities with stringent research guidelines. The facility depends upon animal research for current work on AIDS, cancer and Alzheimer's disease. According to Dr. Kenneth Klivington, assistant to the president at the institute, scientists must submit detailed research plans to the institute's animal welfare committee for project approval.

"It is the responsibility of this committee to consider the validity of the argument for the necessity of using animals, the number of animals needed, and whether the experimental procedures to be used, as well as treatment before and after the procedures, are in accordance with government guidelines and the principles of humane treatment," he said. "Animals are never the first choice as subjects for research. Scientists at the institute use the most modern methods available for biomedical research, and when possible conduct their research with the aid of computer simulations of biological systems and cells grown in laboratory cultures. But when there is absolutely no alternative way to answer important questions, scientists turn to research in animals."

Animals Used in Research

Rats, Mice and Other Rodents ... 85% to 90%

Dogs and Cats ... 1% to 1.5%

Nonhuman Primates ... 0.5%

The remaining percentage includes small numbers of a variety of animal species.

(Source: Office of Technology Assessment Study - *"Alternatives to Animal Use in Research, Testing and Education."*)

The Use and Source of Animal Models

The Office of Technology Assessment estimates that between 17 and 22 million animals are used per year in biomedical research. The majority of these animals, approximately 85 to 90 percent, are rats, mice and other rodents; 1 to 1.5 percent are dogs and cats; .5 percent are nonhuman primates; and the remaining percentage includes rabbits, birds, and domestic and wild animals.

According to the Institute of Laboratory Animal Resources survey, there was a 40% decrease in the number of animals used in research between 1968 and 1978, with the largest decline occurring with nonhuman primates, dogs, cats, and birds.

The reasons for this decrease are complex and include the refinement of research techniques, development of alternatives and a decrease in research funding. Funds for research have failed to increase at the same rate as costs of acquiring and caring for laboratory animals. Researchers have also lowered the incidence of spontaneous disease among lab animals. Today the same research objectives can be obtained with fewer animals because of improved methods for breeding, rearing, genetic control and environmental design.

The overwhelming majority of lab animals are rats and mice bred for this purpose by licensed suppliers. Large animals, such as swine, cattle, and sheep, are supplied primarily by agricultural sources. Most nonhuman primates used in research come from scientific breeding centers, not from the wild.

Many cats and dogs necessary for research are bred for this purpose and others have been abandoned in public pounds and animal shelters. Estimates vary widely, but of the approximately 16.2 to 27 million cats and dogs left in pounds and shelters each year, only about 1.1 percent (approximately 138,000 dogs and 50,000 cats) are used in research annually. The majority of these pound animals, between 10.1 and 16.7 million dogs and cats, are put to death by animal care and control agencies each year, according to the American Humane Association's 1989 statistics. The remaining animals are claimed by their owners or adopted.

While the majority of lab animals are rodents, other species are used in small numbers to provide data not fully available by using rodents. The dog model, for example, continues to assist scientists in discovering new therapies for cardiovascular disease, and in the evaluation of new drugs and surgical techniques. Nonhuman primates, also used in small numbers, help scientists investigate reproductive disorders, hepatitis, deafness, head injuries, and eye disorders in children. Other examples of today's research include the use of mice to study immunology and calves to help improve the performance of artificial heart valves.

"Current laws administered by the FDA do not specify the use of animal testing," said Dr. John Augsburg, assistant to the director of the Center for Veterinary Medicine at the FDA. "However, the FDA position is that the use of animal tests by industry to establish the safety of regulated products is necessary to minimize the risks from such products to humans and animals. Consideration should be given to the use of validated and accepted alternative methods of animal testing. However, many procedures intended to replace animal tests are still in various states of development and it would be unwise for the FDA to urge manufacturers not to do any further animal testing. There appears to be little chance of much replacement of animal testing in the foreseeable future."

Care of Lab Animals - Laws and Regulations

The care of lab animals in universities, medical schools, hospitals, pharmaceutical companies and other research facilities is monitored by the U.S. Department of Agriculture (USDA), under the provisions of the Animal Welfare Act (AWA). The AWA has been amended three times since its passage in 1966. USDA officials make periodic unannounced inspections to ensure compliance with stringent standards for housing, feeding and watering, cleanliness, ventilation and veterinary medical care.

The U.S. Public Health Service (PHS) has an Animal Welfare Policy that applies to all NIH-funded projects involving animals. The NIH requires that the institutions follow the Guide for the Care and Use of Laboratory Animals, prepared by the Institute for Laboratory Animal Resources of the National Research Council. The organization also serves as a scientific forum for laboratory animal medicine and care.

The American Association for the Accreditation of Laboratory Animal Care (AAALAC) offers a lab accreditation program. In addition, the FDA and the Environmental Protection Agency (EPA) have Good Laboratory Practices regulations (GPLs).

The AWA calls for the use of anesthetics and analgesics for potentially painful procedures and for postoperative care. These regulations, along with animal care regulations within each facility, ensure that animals receive the best care and the least pain and distress. USDA statistics state that approximately 95 percent of all lab animals in federally protected facilities are not exposed to pain or distress. Of the remaining percentage, many animals are involved in studies of pain itself, and pain-relieving drugs or anesthetics are administered as soon as possible during the study.

Dr. M.H. Cook, of the USDA's Animal Plant Health Inspection Service (APHIS), said most of the 1,100 USDA-regulated research facilities consistently comply with federal standards, and have often initiated improvements for animal care called for in the AWA amendments before they have become law. APHIS inspectors follow strict guidelines to ensure air temperature, housing and feeding areas, and other regulations are met. "We find that, in general, the scientific community does a good job and is concerned about the care of lab animals," Dr. Cook said.

The most recent amendments to the AWA address animal care and use committee oversight of animal programs. Research facilities have established animal care committees to review laboratory animal care and use issues, including the researchers' consideration of alternatives and the appropriate animal welfare aspects of research procedures. This concept has been a long-standing prerequisite by AAALAC for accreditation.

AAALAC, formed in 1965 and based in Bethesda, MD, is an independent, non-profit organization which offers a peer review accreditation program for research facilities. Dr. Gene New, executive director of the organization, said the 540 facilities accredited by AAALAC point to the concern the biomedical community has for maintaining quality animal care and use.

The AAALAC peer review program is an effective quality control measure, he said. "Accreditation also conveys a 'Gold Standard,' an important criterion for credibility with the public-at-large. The highly regarded AAALAC Accreditation Program is voluntary, but has teeth. It is AAALAC's intent to work with institutions to improve and maintain quality animal programs. However, organizations that do not conform with AAALAC criteria are denied accreditation, allowed to withdraw, or revoked from AAALAC accreditation. Less than 1 percent of the programs evaluated by AAALAC fall into this category."

Animals and Research Statistics

- There are approximately 56 million cats and 54 million dogs in the U.S.
- It is estimated that every hour more than 2,000 dogs and 3,500 cats are born.
- Animal shelters take in 16.2 to 27 million dogs and cats annually.
- Between 10.1 and 16.7 million dogs and cats are put to death in pounds and shelters annually because they were neither claimed by owners nor adopted.
- Approximately 1.1 percent of the dogs and cats from pounds and shelters, that would otherwise be euthanized, are used in research.
- Rats, mice and other rodents comprise 85 to 90 percent of all research animals.
- Only 1 to 1.5 percent of research animals are dogs and cats; and 0.5 percent are nonhuman primates.
- There has been a 40 percent decrease in the number of animals used in biomedical research and testing in the U.S. since 1968.
- Approximately 17 million to 22 million animals are used in research each year.

(Sources: The American Humane Association, USDA, Foundation for Biomedical Research, *Newsweek*)

"The Three R's" and Trends in Alternatives

Most research organizations and scientists are following a practice known as the "Three R's," which stands for replacement, reduction and refinement.

Replacement refers to the use of nonanimal techniques instead of animal models or a lower species of animal when possible. For example, rabbits are no longer used for pregnancy testing, and some preliminary drug toxicity testing can be done using cell cultures, rather than animal species.

Reduction refers to areas where the number of animals used can be reduced. The number of animals used in acute toxicity testing is being reduced as scientists have discovered ways to obtain accurate toxicity data using fewer animals. In addition,

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Feed Costs *continued from page 1.*

Dr. Galligan for more than a year. He has a ration sheet and feeds each cow individually according to her production. The rations formulated for his farm save him about $400 to $500 a month. Dr. Galligan visits the farm periodically to check and to revise the feeding program and to discuss other herd related problems that might arise.

The interactive computer program has five subunits: 1. a nutrient requirement section; 2. a feed bank section that stores nutrient composition of available feed; 3. a computational section where rations are evaluated or formulated; 4. a feeding recipe section, which displays or prints grain mix, mineral mix, total mixed ration, or stanchion barn recommendations; and 5. a comparative economic evaluator, which ranks feeds by a nutritional cost and benefits algorithm.

"We can select up to 12 fixed feed ingredients from a bank of up to 100 feeds," explained Dr. Galligan. "The basis of selection is farm availability and nutrient constraints. Selected variable ingredients are used to balance the ration for dry matter, net energy, crude protein, bypass protein, soluble protein, acid detergent fiber, and neutral detergent fiber. Calcium and phosphorus are balanced using a combination of mineral sources. Trace mineral mixes may be either custom formulated or selected from a bank of proprietary supplements on the basis of limited trace elements in the ration."

The spreadsheet allows individual calculations for the various components. "We can determine what kind of hay to feed if soy meal is high in price," said Dr. Galligan. "If soy meal is low in price, then it will make up a greater part of the ration and the farmer can use first-cutting hay which does not have that great a nutrient value. However, if soy meal is expensive, then we reduce it in the ration formula and recommend that high quality hay be used." This kind of ration formulation requires that farmers change their habits. It used to be that hay was fed in reverse order of harvesting, meaning that the last cut hay was fed first. Now Dr. Galligan recommends that the cuttings be stored separately so the hay can be accurately matched to the other feed ingredients to provide the proper nutrition for the least price.

Other food ingredients are also determined by market prices. If one kind of fiber is high priced, then another may be selected. Further, Dr. Ferguson and Dr. Galligan have encouraged farmers to buy feed in bulk, perhaps as a group. Shotzberger purchases minerals and other feed ingredients jointly with other producers also enrolled in the Production Medicine Services, obtaining a bulk price. Stoltzfus and his neighbor too combine their orders to get a better purchase price. Stoltzfus has taken an additional step to reduce his feed costs, he has installed a diesel-driven roller mill which allows him to mix and prepare his grain mixes. He estimates that this equipment saves him an additional $280 a month.

Drs. Galligan and Ferguson and their colleagues are continually refining the program and the service format. "We are looking at inventory control systems and are making calculations as to whether it is advantageous to buy a three months' supply, versus a six weeks' supply when considering the interest the money could earn if invested alternatively." If all this sounds a bit farfetched coming from veterinarians, it really is not as the contemporary veterinarian has moved beyond being a mere healer. "We have to look at the total farm picture," said Galligan. "While disease prevention is an important part of herd health, management practices also significantly contribute to the cost. The veterinarian can take a look at the overall picture and then advise the client. By increasing the feed efficiency and advising the farmer about ration formulation we can save him more money than through many traditional veterinary services."

The members of the Center for Animal Health and Productivity have been spreading this word at bovine practitioner's meetings and now about 1,000 veterinarians use the program to advise their clients. It costs $100, this includes the spreadsheet, a tutorial and a user's manual as well as a year's subscription to the University's on-line bulletin board. Here users find out about updates and improved features of the program.

The program is also an important teaching tool for Penn's veterinary students, familiarizing them with feed rations and formulation of the most economic ration without sacrificing production yield.

And what is in the future? "We will be looking at the futures market to see if feed expenses can be reduced further," said Dr. Galligan. "We are employing economic principles and models long used in industry and are applying them to agriculture to help the dairy farmer to remain profitable."

Dr. Galligan is an associate professor in animal health economics and holds an MBA degree from the Wharton School. Dr. Ferguson is an assistant professor in nutrition and is board certified in nutrition and reproduction. The ration formulation program was chosen by *Lotus Magazine* as one of the five best applications of Lotus 123 for 1990. The research to develop the program was funded in part by the Pennsylvania Department of Agriculture.

Animal Models *continued from page 5*

scientists can now screen for the efficacy of some potential drugs using the tissue of one animal rather than using hundreds of animals.

Refinement refers to efforts to reduce pain and distress experienced by lab animals. New guidelines from the USDA and NIH are calling for closer scrutiny by researchers in this area, and are encouraging them to investigate additional avenues to measure and reduce pain for animals.

According to Dr. Alan Goldberg, head of the Center for Alternatives to Animal Testing at The John Hopkins University, the Three R's represent the "common definition of alternatives." He said alternative methods in specific cases are scientifically useful, provide a cleaner and more precise result than animal models, and are more economical.

The success of alternatives can be measured by the surge in their use, Dr. Goldberg said. "Ten years ago there were few tissue culture areas in research facilities. Now, every facility that builds a building adds a tissue culture area."

Alternatives most commonly considered are cell, tissue and organ cultures, computer modeling and the use of minimally invasive procedures that produce less stress, Dr. Goldberg noted. While more toxicological research is being conducted in vitro, the potential of culture method in toxicological protocols and hazard assessment is only beginning to be used and evaluated, he said.

Dr. Goldberg attributed the increase of alternatives to public pressure from the animal protection movement. "They've been responsible for encouraging the scientific understanding and development alternatives," he said. "But if the science hadn't been there, it never would have come about."

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Welcome

Each July VHUP and the Widener Hospital welcome new residents and interns. The new residents at New Bolton are: Dr. Julie Anderson (surgery), Dr. Tony Mogg (medicine), Dr. Pam Wilkins (medicine), Dr. Suad Terzich (poultry pathology). Dr. Rochen Love has joined the Widener Hospital as junior surgery clinician. Dr. Fairfield Bain has been appointed lecturer in cardiology.

The new interns at VHUP are: Dr. Lynn E. Babbitt, V'91, Dr. Elizabeth Berger, MN'91, Dr. Lori W. Cabell, TN'91, Dr. Lillian E. Duda, V'90, Dr. Monika Griot-Wenk, Zurich '89, Dr. Kirk A. Hassinger, V'90, Dr. Richard Ian Haworth, Cambridge '91, Dr. Clare Knowler, Glasgow '91, Dr. Nancy Sander, OH '91, Dr. Elaine J. Tobias, V'91, Dr. Susan Westmoreland, V'91. The new VHUP residents are: Dr. Mark Jamba and Dr. Michelle Sabol-Jones, laboratory animal medicine; Dr. Jean Marie Swingle Greek, WI'90, dermatology; Dr. Mary Wilkes, V'91, anesthesia; Dr. Michael G. Conzemuis, IA'90, orthopedic surgery; Dr. Richard A. Rockar, V'88, soft tissue surgery; Dr. Derek Hughes, Liverpool '90, emergency medicine; Dr. Joan Regan, V'79, radiology; Dr. Jamie Anderson, CA-Davis '89, Dr. Mark Elie, MI'85, Dr. Patricia G. Walters, V'90, medicine; Dr. Margaret L. Casals, Zurich '84, medical genetics.

Dr. Ray Boston, formerly at the University of Murdoch, Australia, has joined the Center for Animal Health and Productivity as professor of applied biomathematics. Dr. Daniel Brockman has joined Clinical Studies, Philadelphia, as lecturer in soft tissue surgery. Dr. Andrew Wood from the University of Sydney, Australia, is here as visiting professor of radiology.

Welcome to all!

Promotions and Appointments

Dr. Meryl Littman was promoted to associate professor of medicine; she is chief, Section of Medicine at VHUP. The following were promoted to assistant professors: Dr. Betsy Dayrell-Hart in neurology; Dr. Lesley King in medicine; Dr. Richard Squires in medicine. Dr. Gert Niebauer was reappointed assistant professor in surgery and Dr. Kevin Shanley was reappointed assistant professor in dermatology. Dr. Charles Pugh joined the radiology department in Philadelphia as assistant professor. Dr. Bennett Hershfeld was appointed research assistant professor of ophthalmology.

At New Bolton Center, Dr. Eric Tulleners was promoted to associate professor of surgery and Dr. David Galligan was promoted to associate professor of animal health economics. Dr. Corinne Sweeney was promoted to associate professor of medicine. The following were promoted to assistant professor: Dr. Sue McDonnell to research assistant professor in reproduction; Dr. Ben Martin to assistant professor of equine sports medicine; Dr. Patricia Sertich to assistant professor of reproduction; Dr. Ray Sweeney to assistant professor of medicine; Dr. Wendy Vaala to assistant professor of medicine/neonatology.

Dr. Alan Ruggles has been appointed lecturer in surgery; Dr. Kim Olson has been appointed lecturer in anesthesia, and Dr. Jeff Rubin has been appointed lecturer in Field Service and Reproduction. Mary Lou Shea has been appointed Director of Nursing at New Bolton Center.